Additional Approaches to Treatment of Depression - Reply

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In speaking of enhanced autonomy, we intended to convey that today's patients can independently access medical information and a growing array of products and services, free from physician gatekeeping, that they could not in the past. This modest claim seems indisputable. After all, any interested adult can perform a do-it-yourself electrocardiogram or order a genetic test that screens for 3 specific *BRCA1* and *BRCA2* mutations. Until recently, these tests were available only through a health care professional and were typically limited to patients with a medical indication.

Weinlander appropriately asks whether this new state of affairs is normatively preferable to the previous status quo. Perhaps being able to independently access medical information and take medical actions does not enhance, in the sense of improve, patient autonomy. We agree that physicians must help their patients interpret and understand complex medical information, whether from online sources or direct-to-consumer tests. We also agree that patients' access to information and direct-to-consumer products and services can lead to confusion and uncertainty and that physicians should be prepared to help patients interpret findings and pursue appropriate medical management options. Like Weinlander, we agree that physicians should inquire further before referring or ordering additional tests and screenings. Moreover, physicians should help patients appreciate why additional services are or are not needed, thereby promoting health literacy. In sum, we share Weinlander's view that physicians should not act as mere advisers and gatekeepers but should rather leverage their experience and knowledge to help patients use the available information and resources in ways that benefit them and cohere with their values and goals. The role of physicians may be changing, but it remains both challenging and ethically rich.

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1. Kilbride MK, Joffe S. The new age of patient autonomy: implications for the patient-physician relationship. *JAMA*. 2018;320(19):1973-1974. doi:10.1001/jama.2018.14382

Additional Approaches to Treatment of Depression

To the Editor Dr Cuijpers provided a succinct summary of the many challenges faced by clinicians in the treatment and management of depression.[1] Although depression is one of the most common psychiatric disorders, it is also one the most challenging to treat. I concur with Cuijpers' recommendations for management strategies that optimize what is already known about depression and its treatment and the need for further research on the causes of depression to guide the development of more effective treatments. However, another approach to achieving better treatment outcomes begins with the recognition that some symptoms tend to respond well to most established depression treatments but some do not.

Fatigue, loss of energy, and sleep disturbances are among the most common symptoms of depression before treatment and among the most common residual symptoms after treatment, even among patients who meet standard criteria for remission.[2] For example, in a primary care study, fatigue or loss of energy was reported by 90% and sleep problems by 85% of the depressed patients prior to treatment, and by 35% and 39%, respectively, of patients who no longer met criteria for a major depressive episode after treatment. In contrast, only 21% continued to report the core depression symptoms.[3] Thus, standard treatments for depression may not be as effective for fatigue, loss of energy, and disturbed sleep as they are for most other symptoms of depression. This is especially concerning because these symptoms are also among the best predictors of relapse and recurrent depressive episodes.[4]

Thus, for many patients, the achievement of sustained remission depends on finding better ways to treat these residual symptoms. Promising candidates for augmentation of traditional depression treatments include tailored exercise training, cognitive behavioral therapy for disordered sleep, and melatonin agonists, to name a few. A meta-analysis of studies of cognitive behavioral therapy for insomnia in depressed patients, for example, showed a 3-fold higher likelihood of depression remission compared with control conditions.[5] In current clinical practice, residual symptoms are rarely targeted after the initial treatment of major depression. Research directed toward identifying interventions that improve these symptoms, either concurrent with or following traditional depression treatments, may greatly improve treatment outcomes while a deeper understanding of the causes of depression and the novel treatments that may follow are sought.

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Conflict of Interest Disclosures: None reported.

1. Cuijpers P. The challenges of improving treatments for depression. *JAMA*. 2018;320(24):2529-2530. doi:10.1001/jama.2018.17824

2. Zajecka JM. Residual symptoms and relapse: mood, cognitive symptoms, and sleep disturbances. *J Clin Psychiatry*. 2013;74(suppl 2):9-13. doi:10.4088/JCP.12084su1c.02

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To the Editor In a Viewpoint article, Dr Cuijpers[1] suggested that the priority for improving treatments for depression should be on identifying which patients will respond so that better treatments can be developed. We agree with this call for personalized and precision medicine for depression. However, the author adopted a traditional latent disease model of depression, which is unlikely to accomplish this goal. More specifically, we identify a number of limitations in Cuijpers' arguments.

First, depression is a highly heterogeneous disorder. Based on self-report data, the diagnosis has been assigned to individuals with widely differing sets of problems that are assumed to be the independent expressions of 1 or more latent disease entities. This simplistic medical model has led to the disappointing results summarized in the Viewpoint. More recently, complex network approaches offer an alternative and less restrictive model,[2] with depression being viewed as a set of functionally interconnected problems leading to psychic pain. This approach opens new opportunities for treatment, psychopathology, and nosology.

Second, the identification of processes suggested by the author does not necessitate the development of new treatments. Modern conceptions of empirically supported interventions, such as cognitive behavioral therapy, include a high degree of precision in targeting etiological processes.[3] Examples of treatment processes include attentional retraining, emotion regulation, and interpersonal skill training. A process focus is thus a feature of present-day treatments.

Third, the author mainly based his conclusions on randomized clinical trials that implied the existence of a latent disease entity and did not consider the significant body of literature examining the manner of intervention delivery, known as in-session processes or mediators of outcome. An element of the patient-clinician relationship, the working alliance, shows robust significant associations with symptom improvement,[4] even when taking into account publication bias, source, and timing of alliance assessment. Other processes, such as treatment adherence, possess a larger and stronger evidence base than others.[5]

The field would advance through the adoption of research designs that incorporate more modern analytic methods[2] and track individual patient response to targeted treatment processes. However, research methods that take into account the nested nature of treatment and in-session processes would provide concrete guidance for the practitioner in the optimization of effective treatments.

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In Reply I agree with Dr Carney that focusing on residual and specific symptoms may be another way to improve treatment outcomes, especially because these residual symptoms are one of the best predictors of relapse and recurrent depression.

Drs Kazantzis and Hofmann argue that I used[1] a simplistic model of depression and that depression is a highly heterogeneous disorder. The current model of depression is certainly simplistic, but it is also the model that has been used in the past decades in many thousands of studies on the causes, epidemiology, etiology, and treatments of depression. Furthermore, no alternative model is currently available that can explain the etiology of depression better or that has been shown to result in better outcomes of treatments. Dismissing a model as simplistic is not very useful when no alternative with better empirical support is available.

That depression is highly heterogeneous has been recognized by most researchers for several decades. However, despite many attempts to define subtypes of depression, no subtype has yet demonstrated a differential response to treatments.[2] Network approaches are certainly promising, but no randomized trial has yet shown that applying them results in better outcomes for patients. Many promising innovations have been announced in the past decades, but unfortunately real improvements in outcomes for patients have rarely been seen.

Kazantzis and Hofmann are overly optimistic when they say that psychological interventions have a high degree of precision in targeting etiological processes and minimize the complexities of providing evidence for such processes.[3] Randomized trials can show that a treatment works, but showing how a treatment works is much more difficult and requires large numbers of complicated and expensive studies.[3] These studies have not been done even for well-studied treatments such as cognitive behavioral therapy.[4]

They also seem to consider the correlational findings of in-session processes as strong evidence for how therapies work. Many hundreds of studies have indeed found associations between improvement in patients and characteristics of the therapy. However, because these are only uncontrolled and correlational findings, they cannot be considered as causal evidence.[5] If these processes were as well understood as Kazantzis and Hofmann assume, one would wonder why the overall low response rates to treatments have not improved over time and a relatively small number of patients benefit from them.

As argued in my Viewpoint, substantial progress has been made in the past decades in the research and development of treatments for depression. However, it is also time to recognize that these treatments have limitations and that focused approaches are needed to further reduce the huge disease burden of depression.

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CORRECTION

Numerical Errors and Addition of a Sentence: In the Original Investigation entitled "Association of Genetic Variants in *NUDT15* With Thiopurine-Induced Myelosuppression in Patients With Inflammatory Bowel Disease,"[1] published in the February 26, 2019, issue of *JAMA*, there were numerical errors. In the Results section, Estimated Potential Clinical Effectiveness subsection, second paragraph, the second sentence should be "For every 10 000 patients genotyped, 996 would test positive for a *TPMT* variant and need to receive an alternative therapy to prevent TIM in 81 patients (95% CI, 43-133 patients)." Immediately after, the following should be added: "Genotyping 10 000 patients for *TPMT* would prevent 81 cases of TIM, which is 123 genotyped for every case prevented." This article was corrected online.

1. Walker GJ, Harrison JW, Heap GA, et al; IBD Pharmacogenetics Study Group. Association of genetic variants in *NUDT15* with thiopurine-induced myelosuppression in patients with inflammatory bowel disease. *JAMA*. 2019;321(8):773-785. doi:10.1001/jama.2019.0709

Error in the Introduction: The Research Letter entitled "Trends in First Gabapentin and Pregabalin Prescriptions in Primary Care in the United Kingdom, 1993-2017,"[1] published in the November 27, 2018, issue of *JAMA*, included an error in the Introduction that indicated that gabapentin is approved for migraines and generalized anxiety disorders. The Introduction has been corrected and now indicates that gabapentin and pregabalin are approved for epilepsy and neuropathic pain, gabapentin is indicated, but not approved, for migraines, and pregabalin is approved for generalized anxiety disorders in the United Kingdom. (All other information in the Introduction was correct and is unchanged.) This article has been corrected online.

1. Montastruc F, Loo SY, Renoux C. Trends in first gabapentin and pregabalin prescriptions in primary care in the United Kingdom, 1993-2017. *JAMA*. 2018;320(20):2149-2151. doi:10.1001/jama.2018.12358

Data Error: The Original Investigation entitled "Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial,"[1] published in the November 27, 2018, issue of *JAMA*, had a data error. In the Antidrug Antibodies subsection of the Results, the upper limit of the range of treatment-emergent antidrug antibodies should have been 1280. This article has been corrected online.

1. Banerji A, Riedl MA, Bernstein JA, et al; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA*. 2018;320(20):2108-2121. doi:10.1001/jama.2018.16773

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